TOPICAL MEDICATED BIOADHESIVE COMPOSITIONS AND METHODS OF USE AND PREPARATION THEREOF

The Field of the Invention

This invention relates to topical medicated bioadhesive compositions.

More particularly, the invention concerns such compositions which are specially adapted to use in applying topical medications to human tissue.

In a further aspect, the invention relates to methods for preparation of such bioadhesive compositions.

Background of the Invention

For many years prior to the mid-1980s, medical and dental clinicians had long sought a topical carrier that would adhere tenaciously to human tissue, especially mucosal tissues, that would be chemically compatible with a wide variety of medications and from which such medications would be bioavailable to the underlying tissue. For example, see Stoughton, *Ann. Pharmacol. Toxicol*, 1989, 29:55-69).

The Prior Art

In the mid-1980s, a line of topical medicated bioadhesive products became commercially available and was distributed under the trademark "ZILACTIN®". These compositions, which were disclosed in United States Patents 5,081,157 and 5,081,158 to Pomerantz, formed medicated films on body tissue, which tenaciously adhered to even wet mucosal tissues for up to several hours. The components of these film forming compositions were chemically compatible with a wide variety of medications, which were readily bioavailable from the *in situ* deposited film.

The compositions disclosed by the Pomerantz patents comprised a medicinal component, hydroxypropyl cellulose (HPC), an esterification agent (e.g., salicylic and/or tannic acid) which reacted with the HPC to form a reaction product which was insoluble in body fluids (saliva, etc.), and a volatile non-toxic solvent for the HPC and the reaction product.

Commercial products such as the ZILACTIN® products and a product marketed under the trademark "ORABASE GEL"

(as it was formulated during 1994-1996), which employed the Pomerantz technology and which contained active medications such as topical analgesics (e.g., benzocaine) and topical canker sore medications (e.g., benzyl alcohol) were widely and quickly accepted in the "over the counter" pharmaceutical market.

More recently, a similar product, has appeared, in which ethyl cellulose is used as the film-former instead of the esterified HPC of the Pomerantz formulations. However, this product still contains compounds such as salicylic acid and tannic acid. It is not known whether there is any reaction between the salicylic and tannic acids of these more recent products and the ethyl cellulose. See, e.g., United States Patent 5,885,611 to Church, et al., in which the salicylic acid is alleged to be a "keratolytic agent" and the tannic acid is alleged to be an "astringent."

Still more recently a topical medicated film forming composition has been disclosed in United States Patent 5,955,097 to Tapolsky et al., in which the combination of ethyl cellulose and a bioadhesive polymer is combined in a formulation with an alcoholic solvent and a medicinal

component. It is not known whether such formulations have tissue adhesion properties equal to the Pomerantz formulations, whether these carrier formulations are chemically compatible with a wide variety of medications or whether the medications contained in these formulations are readily topically bioavailable.

Topical carriers known in the art include gels, pastes, tablets, and films. These products, however, may lack one or several of the preferred characteristics for an efficient and commercially acceptable pharmaceutical delivery device. Some characteristics which are desired for topical carriers include water-solubility, ease of handling and application to the treatment site minimal foreign body sensation. Other desired characteristics for an effective, user-friendly product for the treatment of mucosal surfaces include the use of pharmaceutically approved components or materials, initial adhesion to mucosal surface upon application, increased residence time for the protection of the affected tissue or the delivery of the pharmaceutical component, and ease of removal from the affected tissue or natural dissolution of the delivery device at the delivery site.

Gels for application to mucosal tissues and especially the oral cavity are known in the art. For example, U.S. Pat. No. 5,192,802 describes a teething gel made from a blend of sodium carboxymethyl cellulose and xanthan gum. The gel may also have potential use in the treatment of canker sores, fever blisters, and hemorrhoids. However, this type of pharmaceutical carrier has a very limited residence time, given that body fluids such as saliva quickly wash it away from the treatment site. Topical gels are also described in U.S. Pat. Nos. 5,314,914; 5,298,258; and 5,642,749. The gels described in those patents use no aqueous or oily medium and different types of gelling agents.

Denture "adhesive" pastes are also known in the art. However, these preparations are used primarily for their adhesive properties, to adhere dentures to the gums, rather than for the protection of tissue or for the topical delivery of pharmaceuticals, although drugs such as local anesthetics may be used in the paste for the relief of sore gums. U.S. Pat. Nos. 4,894,232 and 4,518,721 describe denture adhesive pastes. The '721 Patent describes a combination of sodium carboxymethyl cellulose and polyethylene oxide in polyethylene glycol.

Pastes have also been used as protectants and as drug delivery systems. One such paste is the product commercialized under the name Orabase®-B, which is a thick paste containing benzocaine for the relief of mouth sores. Ingredients include guar gum, sodium carboxymethyl cellulose, tragacanth gum, and pectin. Even though it does provide numbing to the area of application, the paste is easily displaced from that area and has limited residence time.

Adhesive tablets are described in U.S. Pat. No. 4,915,948. The water-soluble adhesive material used in this device is a xanthan gum or a pectin combined with an adhesion enhancing material such as a polyol. Although residence time is improved with the use of bioadhesive tablets, they are not user friendly, especially for use in the oral cavity, given the unpleasant feelings associated with their solidity, bulkiness, and slow dissolution time. Adhesive tablets are also described in U.S. Pat. Nos. 4,226,848; 4,292,299; and 4,250,163, and are single layer or bilayer devices having an average thickness of 0.2 to 2.5 mm. The adhesive tablets described in these patents utilize a non-adhesive component such as cellulose ether, a bioadhesive

component such as polyacrylic acid, sodium carboxymethylcellulose, or polyvinylpyrrolidone, and a binder for tableting purposes. The cellulose derivatives may or may not be water-soluble. The claimed cellulosic materials in the '299 patent are methyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose.

The use of laminated film "bandages", which are thinner and flexible and therefore give a decreased foreign body sensation, is described in U.S. Patent N. 3,996,934 and 4,286,592. These products are used to deliver drugs through the skin or mucosa. The laminated films, which are thinner and flexible and therefore have a decreased foreign body sensation, is described in U.S. Pat. Nos. 3,996,934 and 4,286,592. The laminated films usually include an adhesive layer, a reservoir layer, and a backing layer. These devices, designed to release drug through the skin at a given rate and over a period of time, are usually not water soluble and are not dissolved or washed away by bodily fluids.

In addition to film systems for the delivery of drug through the skin, film delivery systems for use on

mucosal surfaces are also known. These types of systems, which are water-insoluble and usually in the form of preformed laminated, extruded or composite films, are described in U.S. Pat. Nos. 4,517,173; 4,572,832; 4,713,243; 4,900,554; and 5,137,729. The '173 Patent describes and claims a membrane-adhering film consisting of at least three layers, including a pharmaceutical layer, a layer of low water solubility is made by the combination of one or more cellulose derivatives with a soluble fatty acid of low water solubility, and the intermediate layer is made of cellulose derivatives. The '832 Patent relates to a soft film for buccal delivery, made by the combined use of a water-soluble protein, a polyol, and a polyhydric alcohol such as cellulose and other polysaccharides, and also teaches the use of coloring or flavoring agents. The '243 Patent describes a single or multi-layered thin film made from 40-95% water soluble hydroxypropyl cellulose, 5-60% water-insoluble ethylene oxide, 0-10% water-insoluble ethyl cellulose, propyl cellulose, polyethylene, or polypropylene, and a medicament. The films are three-layered laminates and include an adhesive layer, a reservoir layer, and a water-insoluble outer protective layer.

The '729 Patent teaches a soft adhesive film applicable to the oral mucosa containing a systemic drug and comprising a mixture of a vinyl acetate, water-insoluble homopolymer, an acrylic acid polymer, and a cellulose derivative. Finally, the '554 Patent describes a device for use in the oral cavity having an adhesive layer including a mixture of an acrylic acid polymer, a water-insoluble cellulose derivative, and a pharmaceutical preparation, and a water-insoluble or sparingly soluble backing layer. The adhesive layer contains the pharmaceutical, and upon application to the mucosal surface, delivers the drug to the underlying tissue.

U.S. Patents Nos. 5,081,157 and 5,081,158 describe compositions made of hydroxypropyl cellulose, a non-toxic volatile solvent, an esterification agent which reacts with the hydroxypropyl cellulose to form a reaction product which is soluble in the solvent but not soluble in body fluids at body temperature, and a medicinal component. A crosslinking agent may be used. Following application and air drying, an in situ film forms. As stated in the '158 Patent, "alkyl or hydroxyalkyl substituted cellulose are not suitable substitutes for

hydroxypropyl cellulose" (column 2, lines 28-31) for forming adherent films on body tissues.

Although the '158 Patent admonishes that an esterification agent be included in the composition to effect film formation, the present invention provides a pharmaceutical preparation for application to mucosal surfaces and body tissues, which forms a film upon application to the treatment site without the use of an esterification agent, and thus provides effective drug delivery to the treatment site, surrounding tissues, and other bodily fluids. The film forming components are a water soluble cellulosic polymer, preferably hydroxypropyl cellulose, and a bioadhesive polymer.

SUMMARY OF THE INVENTION

The present invention relates to a mucoadhesive gel for application to mucosal surface and other body tissues, utilizing volatile or diffusing solvents, a water-soluble polymer plus a bioadhesive polymer and a pharmaceutically effective amount of an active pharmaceutical component. Typically, the composition

will have at least one water-soluble hydroxyalkyl cellulose, a bioadhesive polymer, a volatile non-aqueous solvent, and at least one active pharmaceutical. Upon application, the gel forms an adherent, substantive and cohesive film, providing protection to the treatment site. The carrier composition is chemically compatible with a wide variety of pharmaceutical agents from which the agents are bioavailable for delivery of the pharmaceutical to the underlying treatment site, surrounding body tissues, and body fluids. Methods for the protection and localized delivery of pharmaceutical to mucosal surfaces or body tissues are also provided. The gel provides a film having an effective residence time and is easy to apply and use.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, a novel gel carrier composition is formed from hydroxypropyl cellulose and a bioadhesive polymer which adheres to moist body tissue, which serves as a pharmaceutical carrier and which adheres to mucosal surfaces and body tissues. One or more biologically active pharmaceutical compounds are incorporated in the gel.

The present invention finds particular use in the localized treatment of mucosal surfaces and body tissues such as the skin. Upon application to the mucosal surface or skin, the volatile or nonaqueous solvent evaporates, diffuses, or penetrates the surrounding tissues, and a film is formed. The film offers protection to the treatment site, while also providing effective drug delivery to the treatment site, surrounding body tissues, and bodily fluids. Over time, the film slowly erodes away.

The desired properties of the present invention are achieved in the combination of hydroxypropyl cellulose or another pharmacologically acceptable water-soluble polymer, a pharmacologically acceptable bioadhesive polymer, a volatile pharmacologically acceptable solvent and an active pharmaceutical agent. Thickening, coloring, flavoring, or plasticizing agents may also be used. Upon application, the solvent evaporates, diffuses, or penetrates the surrounding tissues, and a film is formed.

Unlike certain gels and pastes known in the art, which have a very limited residence time, given the tendency of bodily fluids such as saliva to wash away the

gel from the treatment site, the present invention offers an increased residence time because of its film persistency and adhesion and its nonaqueous composition. For example, the Orabase® gel is an aqueous based system, and as a result, the film formed upon application is quickly washed away, in a matter of seconds. Unlike the compositions of the Pomerantz '158 patent, which depends on chemical reactions of the components used, the present invention relies on a specific combination of water-soluble and bioadhesive polymers chosen for their desired adhesion and/or film-forming qualities in an appropriate solvent. Importantly, the Pomerantz '157 and '158 Patents teach away from the use of hydroxypropyl cellulose unless it is esterified, teaching that the mechanism of film formation is specific to hydroxypropyl cellulose plus and esterification agent. Despite this teaching, the present invention indeed utilizes soluble alkyl cellulose derivatives such as hydroxypropyl cellulose along with a bioadhesive polymer as the film-forming components in a non-toxic volatile solvent, without the need for an esterification agent.

Also, unlike the mucoadhesive tablets which are known in the art, which offer effective residence time

but also have the disadvantages of discomfort to the use and a foreign body sensation in the oral cavity due to their solidity, bulkiness, and slow dissolution time, the present invention is a gel which offers a very limited and almost nonexistent foreign body sensation.

The residence time of the film formed upon dissipation of the solvent depends on several factors, including the amount of get applied, as well as the components used to make the composition and their relative percentages. Use of polymers with different molecular weights or of different chemical reactivity, for example, may affect the dissolution kinetics of the film. Residence times of up to several hours have been achieved with this invention, depending on the particular formulation. A preferred residence time for effective drug delivery depends on the characteristics of the particular drug, but is at least 1-2 hours. The kinetics of drug release depend on the characteristics of the carrier gel and relative percentages of its components, the total amount of pharmaceutical incorporates into the gel, the particular application site, and the physical and chemical characteristics of the particular drug or combination of drugs.

The pharmaceutical component of the present invention may comprise a single pharmaceutical or a combination of pharmaceuticals, Pharmaceuticals which may be used, either alone or in combination, include anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutic drugs, antibiotics keratolytics, cauterizing agents and antiviral drugs.

Examples of anti-inflammatory analgesic agents include acetaminopen, methyl salicylate, monoglycol salicylate, aspirin, mefanamic acid, flufenamic acid, indomethacin, dielofenac, alcolofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, slidanac, flurbiprofen, fentizac, bufexomac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc.

Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate, tripelennamine hydrochloride,

promethazine hydrochloride, methdilazine hydrochloride, etc.

Examples of local anesthetics include dibucain hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine benzocaine, p-huthylaminobenzoic acid 2-die-ethylamino) ethyl ester hydrochloride, procain hydrochloride, tetracaine, tetracain hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocain dydrochloride, dyclonine, dyclonine dydrochloride, etc.

Examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorbesidine, povidone, cetylpyridinium chloride, eugenol, trimethylammonium bromide, etc.

Examples of vasoconstrictors include naphazonile nitrate, tetrabydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochlroide, etc.

Examples of hemostatics include thrombin, phylonadione, protamine sulfate, aminocaprioc acid, tranexamic acid, carbazochrome, charboxochrome, sodium sulfonate, rutin, hesperidin, etc.

Examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadizine, homosulfamine, sulfaaoxazone, sulfaomidine, sulfamethizole, nitrofurazone, etc. Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromcycin, lincomycin, tetracycline, chlortetracyline, oxytetracycline, metacyline, chloramphenicaol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, etc.

Examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin.

Examples of cauterizing agents include the chloroacetic acids and silver nitrate.

Examples of antiviral drugs include protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protecin

cynthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

Various suitable polymers known in the art for bioadhesive properties are incorporated into the compositions of the present invention. The polymers should be pharmacologically acceptable. Some polymers having bioadhesive properties for use in this invention include polyacrylic acid, cross linked or not, polyvinylpyrrolidone, and sodium carboxymethyl cellulose, alone or in combination.

Permeation enhancers may also be used to improve absorption of the drug at the treatment site. Permeation enhancers for use in this invention include sodium lauryl sulfate, sodium glycopholate, azone, EDTA, sodium cholate, sodium 5-methoxysalicylate, and others known in the art.

The relative percentages of the components materials of the present invention may vary, depending on the type of drug or combination of drugs, the particular target treatment site, the solvent, and the particular polymers

used. Preferably, the solvent or combination of solvents comprise between 50 and 80% by weight of the composition. More preferably, the solvent comprises between 60 and 70% by weight. The active pharmaceutical or combination of pharmaceuticals comprises between 0.1 and 25% by weight, more preferably between 0.2 and 20% by weight. The film-forming gel components should comprise between about 1% and 25% by weight, more preferably between 1% and 10% by weight. The optional flavoring, coloring, or thickening agents and/or permeation enhancer should comprise between 0 and 3% by weight, more preferably between 0.5 and 2.5% by weight.

The characteristics of the film which is formed upon application of the gel, such as thickness, tensile strength, and erosion kinetics, may vary greatly depending on the properties of the tissue to which the gel is applied, the amount of get applied, the amount of saliva or other bodily fluid at the treatment site or surrounding areas, the contact surface, and other physiological factors. However, the properties of the film obtained in vivo may be adjusted via the formulation of the gel, as well as by the addition of plasticizers,

the use of cross linking agents, or the amount of solvent residual.

To make the gel of the present invention, the various components are dissolved in the chosen solvent. Because of the possibility that one or more of the components might not be in solution, a suspension may also be formed. The gelling step may take place at any moment and may be induced by the addition of a special component, a change in pH, a change in temperature, or over time. The solutions and gels may be prepared by various methods known in the art. The gel may be applied to the treatment site by spraying, dipping, by direct application from a suitable dispenser or by finger or swab.

Methods for the treatment of mucosal surfaces and body tissues using the pharmaceutical carrier of the present invention are also provided. In one embodiment, a method for the protection and localized delivery of pharmaceutical to mucosal surfaces or body tissues comprises the steps of preparing the above described film-forming pharmaceutical carrier having at least one water-soluble cellulosic polymer, e.g., hydroxypropyl

cellulose, a bioadhesive polymer, a volatile, nonaqueous solvent, and at least one active pharmaceutical component, and applying the pharmaceutical carrier to the mucosal surface or body tissue by spraying, dipping, or direct application. In the preferred embodiment, the method further comprises the use of hydroxypropyl cellulose, polyacrylic acid, a 95% ethanol and water mixture; and a local anesthetic.

EXAMPLE 1

An ethyl alcohol based gel is prepared using the following components: 65% by weight 95% ethyl alcohol; 0.8% by weight mint flavor; 8% by weight bydroxypropyl cellulose; 2.2% by weight polyacrylic acid; 5% water USP; 15% benzocaine USP; and 4% by weight menthol USP. A clear, yellowish gel with film-forming capabilities is formed.

EXAMPLE 2

An ethyl alcohol/ethoxydiglycol based gel is prepared using the following components: 55% by weight of 95% ethyl alcohol; 1% by weight mint flavor; 8% by weight

hydroxypropyl cellulose; 2% by weight polyacrylic acid; 15% by weight ethoxydiglycol; 15% by weight benzocaine USP; and 4% by weight menthol USP. Here, the mixture of two compatible solvents impacts the time for the film to form. Compared to Example 1, which is a mixture of 95% ethyl alcohol and water as the solvent, the film-forming kinetics of this gel are slower.

EXAMPLE 3

An ethyl alcohol based gel is prepared using the following components: 75% by weight ethyl alcohol, 1% by eight mint flavor, 4% by weight hydroxypropyl cellulose, 3% polyacrylic acid, 9% by weight ethoxydiglycol; and 4% by weight dyclonine. This results in a gel having a stiffer and thicker consistency, which slightly increases the foreign body sensation.

EXAMPLE 4

An ethyl alcohol/1-methyl-2-pyrrolidone based gel is prepared using the following components: 55% by weight of 95% ethyl alcohol; 1.5% by weight mint flavor; 26% by weight 1-methyl-2-pyrrolidone; 6% by weight hydroxypropyl

cellulose; 2.5% by weight polyacrylic acid; 5$ by weight water; and 4% by weight menthol USP. Because methyl pyrrolidone has undesirable taste, a higher percentage of flavoring agent is used to mask the taste. The kinetics of diffusion of this gel are appropriate and allows for the formation of an effective film.

EXAMPLE 5

An ethyl alcohol based gel is prepared, using polyvinyl pyrrolidone as a bioadhesive polymer. The components are as follows: 65% by weight 95% ethyl alcohol, 0.8% by weight mint flavor, 6.2% by weight hydroxypropyl cellulose, 4% by weight polyvinyl pyrrolidone, 5% by weight water USP, 15% by weight benzocaine USP, and 4% by weight menthol USP. The use of polyvinyl pyrrolidone instead of polyacrylic acid as the bioadhesive polymer results in the formation of an effective film, but adhesion is weaker than that achieved with the use of polyacrylic acid.

EXAMPLE 6

An ethyl alcohol based gel is prepared, using sodium carboxymethyl cellulose as a bioadhesive polymer. The components are as follows: 75% by weight of 95% ethyl alcohol, 1% by weight mint flavor, 8% by weight hydroxypropyl cellulose, 4% by weight sodium carboxymethyl cellulose, 8% by weight water USP, and 4% by weight menthol USP. The use of sodium carboxymethyl cellulose instead of polyacrylic acid results in a weaker adhesion.

EXAMPLE 7

An ethyl alcohol based gel is prepared using the following components: 78% by weight of 95% ethyl alcohol, 1% by weight mint flavor, 8% by weight hydroxypropyl cellulose, 3% by weight polyacrylic acid, 6% by weight water USP, 0.1% by weight sodium lauryl sulfate, and 3.9% by weight dyclonine USP. The gel formed is comparable to that of Example 1. However, the use of a different anesthetic, dyclonine instead of benzocaine, results in a less intense numbing effect.

EXAMPLE 8

A gel according to the formulation of Example 1 is prepared and is administered to eight healthy volunteers. Participants are directed to apply a very small quantity of the gel to the tip on one finger and then to place and quickly spread/rub the gel at one location in the oral cavity. The volunteers are asked to describe, on a scale of 0 to 3 (with 3 being very good, 2 good, 1 fair, and 0 poor), the ease of handling of the gel, and its numbing effect. The volunteers are also asked to describe the time necessary for the formation of a film at the site of application, as well as its residence time, and whether or not they experienced a foreign body sensation. Additionally, the volunteers are asked to describe as positive (+) or negative (-) their impressions of the taste and overall efficiency of the gel, as well as their overall impression of the gel. The results are provided in Table 1 below.

TABLE 1

No.	Handling	Time for film to form	Residence Time	Numbing Effect	Taste	Efficiency	Foreign Body Sensation	Overall Impression
1	3	<30 sec	~ 1 hr	3	+	+	minor	+
2	2	< 1 min	~ 1 hr	2	-	+	none	+
3	3	<30 sec	~ 2 hr	2	-	-	minor	-
4	3	< 1 min	~ 2 hr	3	-	-	none	-
5	3	< 1 min	~ 3 hr	2	+	+	yes	+
6	2	<30 sec	~ 1 hr	2	+	-	yes	+
7	2	< 1 min	~ 2 hr	3	-	+	none	-
8	3	< 1 min	~ 2 hr	2	+	-	minor	+

The formulation of Example 1 will be easy to apply and will rapidly forms film, while providing only a minimal foreign body sensation to the user. The film will stay in place long enough to provide effective drug delivery, while also providing effective numbing to the treatment site and surrounding tissues.

Having described my invention is such terms as to enable those skilled in the art to understand and practice it and, having identified the presently preferred embodiments thereof, I CLAIM: